NTP
National Toxicology Program

Draft NTP Monograph on Health Effects of Low-level Lead:
Cardiovascular Effects

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Cardiovascular Effects

- Principal health effects of Pb
  - Increased blood pressure and risk of hypertension
  - Increased risk of mortality from cardiovascular causes
  - Other cardiovascular effects considered include heart rate variability, electrocardiogram abnormalities and clinical cardiovascular disease
- EPA and ATSDR conclude Pb
  - Increases blood pressure
  - Increases deleterious cardiovascular outcomes

Blood Pressure and Hypertension

- Outcomes considered
  - Systolic blood pressure (pumping phase)
  - Diastolic blood pressure (relaxing phase)
  - Hypertension (systolic ≥140 or diastolic ≥90)

NTP conclusion: *sufficient* evidence that blood Pb levels <10µg/dL are associated with increased blood pressure and risk of hypertension

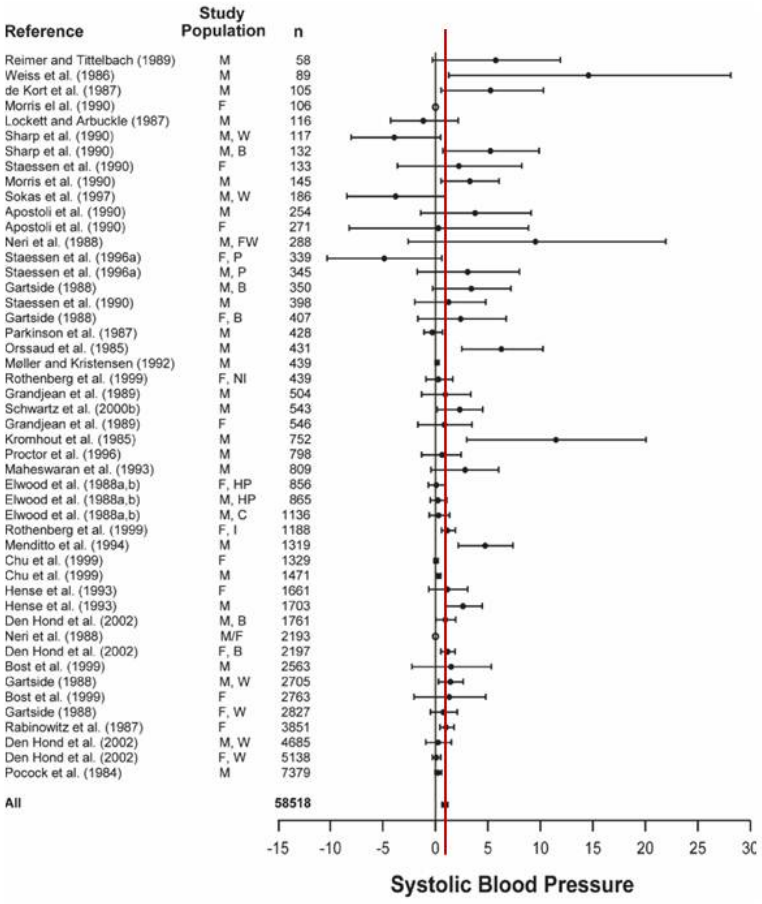
Blood Pressure and Hypertension – Evidence

NTP conclusion: *sufficient* evidence <10µg/dL based on:

- Published meta-analyses
  - Blood and bone Pb associated increase in blood pressure
  - Bone Pb associated increase in risk of hypertension
  - Analyses include blood Pb >10µg/dL
- Numerous studies of blood Pb support an association with increased blood pressure and risk of hypertension
  - NHANES 1999-2006: 16,222 adults blood Pb ≤10µg/dL (Scinicariello *et al.* 2011)
- **Supported by**
  - Consistent support for an association of bone Pb
  - Animal data show that low Pb exposures increase blood pressure

Meta-Analysis: Nawrot, 2002

- EPA 2006 AQCD Figure 6-10: Change in the systolic pressure (effect estimate in mm Hg) associated with a doubling of the blood lead concentration
- Studies arranged vertically by increasing study size.



Blood Pressure and Hypertension – Life Stages

- Pregnant Women

  NTP conclusion: *sufficient* evidence <10µg/dL based on:
  - All 7 studies identified support an association of blood Pb with increased blood pressure during pregnancy and with gestational hypertension

- Children

  NTP conclusion: *inadequate* evidence
  - Few studies in children
  - Inconsistent results

- Menopausal Women

  NTP conclusion: *inadequate* evidence
  - Few studies focused on menopausal women
  - Inconsistent results

Table 6.8: NTP conclusions on cardiovascular effects of low level Pb				
Health Effect	**Population**	**Conclusion**	**Blood Pb Evidence**	**Bone Pb Evidence**
Blood Pressure and Hypertension	Adults	*Sufficient*	Yes, <10µg/dL	Yes
	Children	*Inadequate*	Unclear	Yes (one study)
	Pregnant Women	*Sufficient*	Yes, <10µg/dL	Not studied
	Menopausal Women	*Inadequate*	Unclear	Not studied

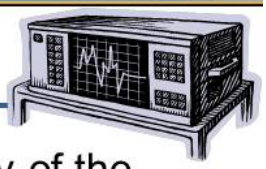
Heart Rate Variability

- Decreased variability is a marker of abnormal autonomic nervous system functioning

NTP conclusion: *inadequate* evidence

- Few studies of blood Pb and heart rate variability
- Inconsistent results

Electrocardiogram Abnormalities



- Changes in the typical pattern of electrical activity of the heart as measured by electrocardiogram (ECG)

NTP conclusion: *limited* evidence <10µg/dL

limited evidence <5µg/dL

- **Men**: Normative Aging Study associated bone Pb and ECG abnormalities (Cheng *et al*. 1998, Park *et al*. 2009, Eum *et al*. 2011)
- **Children**: Oswego Children's Study found blood Pb associated with decreased stroke volume and total peripheral resistance (Gump *et al*. 2005, 2007, 2011)

Clinical Vascular Disease

- Outcomes considered
  - Peripheral artery disease – impaired flow to the limbs
  - Coronary artery disease – impaired flow to the heart
  - Cerebral vascular disease – impaired flow to the brain
  - Myocardial infarction – damage to the heart muscle
  - Stroke – damage to brain tissue

NTP Conclusions: *limited* evidence that blood Pb <10µg/dL and <5µg/dL is associated with risk of any type of clinical disease

and *inadequate* evidence for a specific diagnosis of clinical disease

General Clinical Vascular Disease - Evidence

NTP Conclusions: *limited* evidence <5µg/dL based on:

- Coronary heart disease
  - Normative Aging Study men associated (Jain 2007)
  - Former Pb workers and Glostrup Population Study not associated (Kim, 2008; Møller, 1992)
- Peripheral artery disease
  - NHANES 1999-2002 adults over 40 associated (Gualler, 2006)
- Measures of arterial function
  - finger blood flow (Ishida 1996 and Kaewboonchoo, 2010)
  - increased thickness of common and carotid arteries (Zeller, 2010)
- **Supported by**
  - Animal data on an atherogenic effect of Pb on vascular tissue and smooth muscle cells

Specific Clinical Diseases - Evidence

NTP Conclusions: *inadequate* evidence for specific diagnoses based on:

- Lack of replication for specific diseases or markers of vascular function

Cardiovascular Mortality

NTP conclusion: *sufficient* evidence that blood <10µg/dL is associated with increased mortality from cardiovascular causes, based on:

- Large prospective studies with 12-14 years of follow up
  - NHANES III - blood Pb was associated (Menke *et al.* 2006)
  - Normative Aging Study – bone Pb was associated, but blood Pb was not (Weisskopf *et al.* 2009)
  - Glostrup Population Study – blood Pb was not associated with any type of mortality (Møller *et al.* 2002)
- Cardiovascular effects of Pb on hypertension, blood pressure, and cardiovascular disease support biological plausibility

The NTP's Conclusions for Cardiovascular Effects

There is *sufficient* evidence that blood Pb levels <10µg/dL in adults are associated with adverse effects on cardiovascular function and there is *inadequate* evidence to evaluate cardiovascular effects in children.

Specific Cardiovascular Charge Questions

i. Please comment on whether the scientific evidence presented supports the NTP's conclusions.

ii. Please comment on whether you agree/disagree with the NTP's conclusions. Explain why. Identify any references that should be cited.

a. Blood pressure and hypertension
b. Heart rate variability
   Electrocardiogram (ECG) abnormalities
   Clinical cardiovascular disease
c. Cardiovascular mortality

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	Children	*Inadequate*	Unclear	Yes (one study)
	Pregnant Women	*Sufficient*	Yes, <10µg/dL	Not studied
	Menopausal Women	*Inadequate*	Unclear	Not studied
Heart Rate Variability	Adults	*Inadequate*	Unclear	Yes (one study)
Electrocardiogram Abnormalities	Men	*Limited*	No	Yes (one study)
	Children	*Limited*	Yes, <5µg/dL (one study)	Not studied
Clinical Cardiovascular Disease (General)	Adults	*Limited*	Yes, <5µg/dL	Yes (one study)
Clinical Cardiovascular Disease (Specific)	Adults	*Inadequate*	Unclear	Yes (one study)
Cardiovascular Mortality	Adults	*Sufficient*	Yes, <10µg/dL	Yes (one study)

d. Other cardiovascular effects

i. Please comment on whether there are additional cardiovascular effects in humans that may be adversely affected by low-level Pb exposure that you would recommend adding to the document.

Please comment on whether and how the additional cardiovascular effects would affect the overall conclusions for health effects associated with blood Pb levels <10µg/dL.

A. General Questions

1) Is the text in the draft monograph articulated clearly and correctly? Are the summary sections useful? Are the tabular information and format easily understandable? If not, please identify the specific sections that need improvement and provide specific suggestions for improvement.

2) Is the information in the draft monograph's text and tables presented objectively?
If not, please identify the specific sections that need improvement and provide specific suggestions for improvement.